Global Harmonization Task Force

Proposed Document

Title:	**Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy**
Authoring Group:	**GHTF Study Group 4: Auditing**
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Preface

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide non-binding guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

1 Introduction

The purpose of this document is to give guidance to regulatory auditing organizations and to auditors for conducting medical device quality systems regulatory audits (audits) based on the process approach to quality management of ISO 13485:2003 and 21 CFR Part 820. The audit strategy can be seen as guidance on how to audit the effectiveness of quality systems in a systematic and effective manner within a reasonable time. This includes the fulfilment of regulatory requirements of medical device manufacturers. The main aim of the guidance is to promote audit consistency – a necessity for harmonization and mutual recognition of audit results.

Benefits for the regulators include:

- Improved auditing, leading to improved quality systems and product quality
- Achievement of greater consistency in regulatory audits both among auditors within a regulatory organization and between regulatory organizations
- Promotion of greater collaboration between regulators in regard to regulatory audits
- Increased confidence in audits performed by a regulatory organization and acceptance of those audits by other regulators
- Saving of resources
- Guidance for new emerging countries

Benefits for the manufacturer of medical devices include:

- Improved auditing, leading to improved quality systems and product quality
- Achievement of greater consistency in regulatory audits
- Saving resources through easier preparation for regulatory audits
- Reducing the number of times a single manufacturer undergoes audits by different regulatory bodies
- Increased confidence in and acceptability of audits by other regulators

Beneficiaries also include the operators of medical devices and patients, who can have high degree of assurance that medical devices placed on the market will be safe and effective.

Comments or questions about the use of this guidance document should be directed either to the Interim Chair of SG 4 or to the Secretariat of SG4 whose contact details may be found on the GHTF web page (www.ghtf.org).

2 Scope

This document is intended to be used by regulatory auditing organizations and auditors as a guide for conducting medical device quality systems audits based on the process approach to quality management of ISO 13485:2003 and 21 CFR Part 820.

Additional regulatory requirements and guidance will need to be considered, depending on the regulatory authorities who will receive and use the audit report (see "Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 3: Regulatory Auditing Report" (SG4/N33) under preparation).

This guidance document applies to initial audits and to surveillance audits as they are defined in "Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements" (SG4/N28R2) – including the supplements – developed by GHTF Study Group 4 as a guide for auditing organizations.

3 References

GHTF/SG4/N28R2: Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements (1999)

GHTF/SG1/N011R16: Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)

21 CFR Part 820 – Quality System Regulation (June 1, 1997)

Guide to Inspections of Quality Systems (QSIT); Food and Drug Administration – August 1999

ISO 13485:2003: Quality systems – Medical devices – System requirements for regulatory purposes

ISO 19011:2002: Guidelines for quality and/or environmental management systems auditing

ISO/TC 210/WG1 N62: Guidance on the Application of ISO 13485:2003

ISO/IEC Guide 62: 1996(E) General requirements for bodies operating assessment and certification/registration of quality systems. International Organization for Standardization, case postale 56, CH-1211 Geneva 20, Switzerland.
International Electrotechnical Commission, case postale 131, CH-1211 Geneva 20, Switzerland.

IAF Guidance on Application of ISO/IEC Guide 62, Issue 2 (July 2002)

ISO 14971:2000 "Medical devices – application of risk management to medical devices"

4 Definitions

Audit
Systematic independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled.
ISO 19011:2002

Note: For the purpose of these guidelines, "audit" means a regulatory audit

Regulatory audit
The audit of a quality system to demonstrate conformity with a quality system standard and the relevant regulatory requirements.

Audit criteria
Set of policies, procedures or requirements.
ISO 19011:2002

Audit evidence
Records, statements of fact or other information, which are relevant to the audit criteria and verifiable.
ISO 19011:2002

Note: Audit evidence may be qualitative and/or quantitative and is used to substantiate audit observations

Technical files
See document of GHTF/SG 1"STED, Summary Technical Documentation", proposed document SG1/N011R16 of 2001.

Medical device
Medical Devices are defined in the national and regional regulations listed in appendix B of the GHTF document SG 4/N28 R2: "Guidelines for Regulatory Auditing of quality Systems of Medical Device Manufacturers – Part 1: General Requirements".

Process
Set of interrelated or interacting activities which transforms inputs into outputs
ISO 9000:2000

Regulatory requirements
For the purpose of these guidelines any part of a law, ordinance, decree or other regulation, which applies to quality systems of medical device manufacturers.
SG4/N28 R2: "Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements".

Note: Guidelines, notes, draft documents, or the like should not be used as regulatory documents and are not to be construed as such unless formally promulgated.

5 General Remarks on Regulatory Auditing Strategy

Conducting the regulatory audit, the quality management system of a medical device manufacturer based on ISO 13485:2003: "Quality systems – Medical devices – System requirements for regulatory purposes" or based on 21 CFR Part 820 is checked with regard to conformity with the quality system requirements and compliance with the relevant regulatory requirements.

5.1 Objectives of a Regulatory Audit

Based on the definition of a regulatory audit the auditing organization determines during a regulatory audit the compliance of the auditee's quality system with the relevant regulatory requirements. The audit checks how quality problems associated with a medical device or the quality system are recognized and settled.

The audit should be planned and conducted in such a way that the following objectives are reached:

- The effectiveness of the manufacturer's quality system – including the fulfilment of regulatory requirements - is measured and monitored in a systematic and effective manner within a reasonable time.
- The regulatory audit is process-oriented. The application of a system of processes within an organization, together with the identification and interactions of these processes, and their management, can be referred to as the "process approach". Therefore, the audit should preferably follow the workflow processes of the medical device manufacturer.
- The regulatory audit is risk-based with a focus on key processes of the quality system necessary to manufacture the medical devices. In other words the auditor should concentrate on factors that are most likely to affect patient safety.
- The audit is transparent to the auditee.
- The audit process and results are similar regardless of which auditing organization or individual auditors conduct the audit, with an ultimate goal for harmonization and mutual recognition of audit results.

5.2 Auditing Quality Management Systems and Subsystems

Rather than focusing on the individual requirements of the standard, an audit should focus on the overall effectiveness of the quality management system. To break the audit into more manageable parts, key activities or subsystems have been identified. These subsystems are based in part on the Quality System Inspection Technique (QSIT) developed by the U.S. Food and Drug Administration (FDA) with input from the medical device industry. The GHTF Study Group 4 identified additional subsystems (3, 6, 7 and 8 in Table 1).

The subsystems and associated clauses of ISO 13485:2003 and 21 CFR Part 820 are:

Subsystem	Clauses and secondary clauses (linkages) of ISO 13485:2003	Clauses of 21 CFR Part 820
1. Management	4, 5, 6, 8	820.5, 820.20, 820.22, 820.25
2. Design and development	7	820.30
3. Technical files	4, 7	820.30, 820.181, 820.50*
4. Production Processes	6, 7, 8	820.50, 820.70, 820.72, 820.75, 820.80, 820.90, 820.20, 820.25, 820.30, 820.40, 820.100, 820.180
5. Corrective and preventive actions	4, 5, 6, 7, 8	820.90, 820.100, 820.198, 820.250, 803
6. Purchasing controls	7	820.50, 820.80
7. Documentation and records	2, 4	820.40, 820.180, 820.100, 820.181, 820.184, 820.186, 820.198, 820.200
8. Customer requirements	7, 8	820.30, 820.100, 820.198
Appendix 3: Sterilization Process	7, 8	820.50, 820.70, 820.72, 820.75, 820.90, 820.100, 820.140, 820.150, 820.184

Table 1: Subsystems and associated clauses

More detailed references to clauses and subclauses of ISO 13485:2003 and 21 CFR Part 820 are given in chapter 6.0: Auditing subsystems

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* FDA does not require "Technical files". However, when checking technical files, an auditor also may verify that a manufacturer complies with certain requirements in Quality System Regulation, 21 CFR Part 820.

The key subsystems for addressing quality are the subsystems 1 to 5 identified in Table 1. These should receive the primary focus of the audit. It may be appropriate to treat the other subsystems as key subsystems in some situations. Examples for the subsystem purchasing controls include:

- A "virtual manufacturer" who contracts essential activities such as design and production
- A manufacturer who contracts a sterilization process, or
- A manufacturer of high risk medical devices who purchases significant components and subassemblies.

5.3 Auditing Approaches

There are different approaches to conducting a regulatory audit:

- The "**top-down**" approach for conducting a regulatory audit begins with an evaluation of the structure of the quality management system and its subsystems: management, design control, technical files, production processes, and corrective and preventive actions. Selected subsystems are reviewed to determine whether the manufacturer has addressed the basic requirements by defining and documenting appropriate procedures. It is important to check that a process approach is applied both in the quality system and in each subsystem, e.g. by using a PDCA cycle (see Chapter 5.4). With the "top-down" approach, the auditor will first confirm that the manufacturer has established appropriate procedures and policies. Then the auditor will review evidence including records to verify whether the manufacturer is implementing the procedures and policies effectively and the quality system is in conformity with regulatory requirements.

  The advantage of this approach is a uniform approach for a systematic and transparent regulatory audit process – both for the regulatory sides and the manufacturer.

- The „**bottom-up**" approach for a regulatory audit can have as a starting point a quality problem; e.g., a medical device report of an adverse event or nonconforming product. Thus, the auditor starts at the bottom and works his way through the manufacturer's quality system up to the management responsibility.

  The advantage of this approach is a quick insight on the effectiveness of the selected subsystems and processes that have been affected by the specific quality problem and the cause(s) of the quality problem. The disadvantage of this approach is that it is very difficult for the auditor to determine how effectively the complete quality system works.

- A third alternative is a **combination** of these two approaches. The auditor starts by reviewing the top layer of the quality system (top-down); then audits some aspects

of the implementation of the system (e.g., the production process) and finally the auditor verifies that the relevant procedures are being used (bottom-up). The advantage of the combination approach is that it is often quicker to audit than using either the top-down or bottom-up approach. The combination approach also offers more flexibility in identifying the cause(s) of specific problems while assessing the effectiveness of the quality management system.

Depending on the purpose and trigger of an audit, an appropriate approach should be selected. If there are no special events to be covered during the audit , the top-down approach is preferred. An initial audit will normally follow a top-down approach. Audits which include a potential significant safety issue will normally follow a bottom-up approach.

5.4 Process Based Auditing

Any effective quality management system (including the subsystems) works as a control process, which has the ability to detect deviations and nonconforming products and assures that the corrective and preventive action measures are effective. The regulatory auditor should check that all subsystems and processes of the quality management system are structured as self-regulating control processes. For example Deming's PDCA cycle demonstrates such a process with the following components:

- **Plan**
  Has the manufacturer established the objectives and processes to enable the quality system to deliver the results in accordance with the regulatory requirements?
- **Do**
  Has the manufacturer implemented the quality system and the processes?
- **Check**
  Has the manufacturer checked process monitoring and measurement results against the objectives and the regulatory requirements? Does the manufacturer evaluate the effectiveness of the quality system periodically through internal audits and management reviews?
- **Act**
  Has the manufacturer implemented effective corrective and preventive actions? Confirm that the company is committed to providing high quality safe and effective medical devices, and that the company is conforming with applicable laws and regulations.

These are generic questions that can be asked throughout the audit.

5.5 Sampling

In general there are two ways of sampling records for review which are useful in regulatory audits – risk based and statistical. Where possible, auditors should select samples based on factors which are most likely to affect the safety of the patient. In this situation sampling tables are not necessary. The auditor may however decide to select a statistically valid sample. In this case, the **Tables 1** or **2** from **Appendix 1** should be

used. A sample can also be drawn using a combination of risk based and statistical sampling.

5.6 Audit Planning

Further to the requirements given in the chapter 11 of GHTF Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements (SG4/N28R2), some more consideration should be given to the following points:

- Information from the manufacturer
- Estimation of audit duration, frequency and targeted on-site auditing time

Further points to consider are given in chapter 6.

A) Information required from the manufacturer

In the planning phase, the following information should be requested from the manufacturer to estimate the audit duration and to prepare the audit plan as described in GHTF Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements, clause 11.1.2 (SG4/N28R2)

a) manufacturer's name, address
b) contact name, telephone, fax numbers and e-mail addresses
c) total number of employees (all shifts) covered by the scope of the audit
d) range and class of medical devices being manufactured
e) types of devices sold and/or planned to be sold in the countries and/or regions for which the regulatory requirements will be assessed, including a complete list of authorizations (e.g. licenses) issued for those devices (where applicable)
f) location and function of each site to be included in the audit
g) a list of activities on each site
h) the involvement of any special manufacturing processes, e.g. software, sterilization, etc.
i) a list of the activities performed by subcontractors and their locations, including the type of control that is exercised over those out sourced operations
j) any existing audit results from other auditing organizations e.g. from USA, Australia, Europe, Canada, Japan.
k) do they install or service the medical devices produced
l) changes since the last audit, if applicable.

B) Estimation of audit duration, frequency and targeted on-site auditing time
Audit frequency

The audit frequency is dependent on the factors mentioned in clause 8 (Types of audits) of GHTF Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements (SG4/N28R2), the regulatory requirements and history of the manufacturer.

Audit duration

The audit duration has a significant effect on both regulatory agencies and industry. It is dependent on factors such as the audit scope and specific regulatory requirements to be

assessed, as well on the range, class and complexity of devices, and the size and complexity of the manufacturer.
If not specifically mentioned, the considerations in this section are applicable to initial, and surveillance-audits.

Relation between audit frequency and audit duration
Audit duration depends on the audit frequency. In the following an annual audit frequency is the baseline as reference in IAF Guidance on the Application of ISO/IEC Guide 62. For more or less frequent audits, audit duration should be adapted accordingly.

Method of estimating audit duration
When auditing organizations are planning regulatory audits, sufficient time should be allowed for the audit team to establish the conformity status of a medical device manufacturer's quality system with respect to the relevant regulatory requirements. Any additional time required to assess national or regional regulatory requirements must be justified.

The table from the IAF Guidance on the Application of ISO/IEC Guide 62 may be used in order to establish a baseline initial audit duration for ISO 9000-series, measured in auditor-days. As this table is not intended for the special needs of medical device audits, additional time should be added for the requirements of ISO 13485:2003 and for regulatory requirements. This document also provides guidance for other types of activities, such as surveillance audits.

The baseline includes time to prepare for the audit, preview the quality system documentation and write the report. It does not consider the time required for design dossier reviews, type examinations, pre-market approvals and other similar activities. The baseline for initial audits should be adjusted to take into account the other types of audits and the factors listed in **Appendix 2** which may increase or decrease the estimated audit duration, but only if these factors are required by the applicable regulations.

Targeted on-site auditing time
The targeted on-site time to complete the initial auditing of the subsystems should be based on the following dates given in Table 2:

Subsystem	Targeted time	Remarks
Management	5-10 %	
Design and development controls	0-20%	Depends on regulatory requirements
Technical files	5-20%	
Production processes	20-30 %	
Corrective and preventive actions	10-30 %	
Purchasing controls	5-20%	More time for virtual manufacturers
Documentation and records	5 %	
Customer requirements	5 %	

Table 2: Targeted on-site auditing time

The targeted on-site audit time for each subsystem will vary depending on factors such as:

- the audit scope
- schedule changes
- the gathering of information from remote locations

5.7 Guidance for Logistics during an Audit

The following points should help the auditor in performing the audit in the most appropriate way:

- Does the manufacturer have changes (e.g. organization, quality system, facilities, processes, products) to present during the opening meeting?

- Limit the disturbance of the CEO and Executive Management to a minimum and be flexible in auditing Management Responsibility.

- Follow-up issues from last audit as soon as possible, to determine whether the manufacturer has effectively implemented corrective actions.

- Auditing the warehouse at the beginning of an audit allows for the selection of examples that can be followed up later on (e.g. nonconforming material, batch records, etc.)

- Auditing traceability at an early stage of the audit allows the traceability path to be followed either forward (e.g. simulated recall) or backwards, and gives the manufacturer sufficient time to access relevant information or to carry out the necessary actions.

- For surveillance audits focus either on design and administrative processes or on production and related activities.

- Internal audits, complaints, CAPA and management review should be covered at every audit.

- Auditing documentation and training at the end of an audit allows for better follow-up of the examples picked-up during the audit.

- The local situation may influence the sequence of audit and should be considered to avoid wasting time.

Consideration to those points should be given, but the audit team is free to audit the subsystems in any sequence appropriate.

5.8 Linkages

Although most of the auditor's time will be spent on examining processes within the sub-systems, it is important to remember that links exist between the sub-systems and between different processes. Some of these links are less obvious than others, but should be checked during the audit.

Examples

Link between:

- Corrective and preventive actions and management: Disseminating CAPA information to management for management review
- Design and development controls and purchasing controls: Design output used in evaluating potential suppliers of components and assemblies and communicating specified purchase requirement to that supplier.

Within a process, the steps will normally be linked because the output from one step will be the input to the next. During a process based audit, these links may be picked up automatically by the auditor.

There are also some obvious links between processes, e.g. the output from design will be an input to production. These links need to be checked during both parts of the audit (e.g. design and production) to verify that the link is working and the quality system is working as a coherent whole.

There are other links which may be less obvious, but which still need to be audited, e.g. if non-conforming product is seen in finished goods, did this problem originate in stores, production, final inspection or design?

There also are links between sub-systems, e.g. if faulty components arrive on the production floor, was this caused by the supplier, receiving inspection, incorrect data to the supplier or by design?

In such instances, does the system require the manufacturer to always make a CAPA report?

6.0 Auditing subsystems

There is a specific goal in auditing each subsystem. The plan for auditing each subsystem should be process based (chapter 5.4) and should enable the goal to be reached. This should include verifying conformance with the requirements which affect each subsystem. For logistics see also chapter 5.7

Note 1: Numbers beneath each chapter refer to ISO 13485:2003 and 21 CFR Part 820.
Note 2: Chapters marked with* are main subsystems and should receive a main focus of the audit, if this is a regulatory requirement. See also chapter 5.2.

6.1 Management *

GOAL: The purpose of the management subsystem audit is to evaluate whether top management ensures that an adequate and effective quality system has been established and maintained.

Major Steps: The following major steps serve as a guide in the audit of the "Management" subsystem:

1. Verify that a quality manual, management review and quality audit procedures, quality plan, and quality system procedures and instructions have been defined and documented.
   ISO 13485:2003: 4.1, 4.2;
   21 CFR 820.20(c), 820.20(d), 820.20(e) , 820.22

2. Verify that a quality policy and objectives have been defined and documented and steps taken to achieve them.
   ISO 13485:2003: 5.3, 5.4
   21 CFR 820.20(a)

3. Review the manufacturer's established organizational structure to verify that it includes provisions for responsibilities, authorities (e.g. management representative), resources, competencies and training
   ISO 13485:2003: 5.1, 5.5.1, 5.5.2, 6.1, 6.2,
   21 CFR 820.20(b), 820.20(b)(1), 820.20(b)(2), 820.20(b)(3)(i) and (ii), 820.25

4. Verify that management reviews, including a review of the suitability and effectiveness of the quality system, are being conducted.
   ISO 13485:2003: 5.6
   21 CFR 820.5, 820.20(c)

5. Verify that internal audits of the quality system are being conducted including verification of corrective and preventive actions.
   ISO 13485:2003: 8.2.2
   21 CFR 820.22

In conclusion of the audit of the other subsystems a decision should be made as to whether top management has taken the appropriate actions to ensure a suitable and effective quality system is in place.

6.2 Design and Development *

GOAL: The purpose of auditing the design and development subsystem is to determine whether the design process is controlled to ensure that devices meet user needs, intended uses and specified requirements.

Major Steps: The following major steps serve as a guide in the audit of the "Design and Development" subsystem:

1. Verify if products are subject to design and development procedures.
   ISO 13485:2003: 7.1
   21 CFR 820.30(a)

2. Select design project(s)
   Criteria for selection:
   - single product focus
   - risk based
   - based on complaints or known problems
   - most recent project
   - cover product range

3. Review the design plan for the selected project to understand the layout of the design and development activities, including assigned responsibilities and interfaces.
   ISO 13485:2003: 7.3.1
   21 CFR 820.30(b)

4. For the design project(s) selected, verify that design control procedures and risk management procedures have been established and applied.
   ISO 13485:2003: 7.3.1
   21 CFR 820.30(a), 820.30(c) – (j)

5. Confirm that design inputs were established and address customer functional, performance and safety requirements, intended use, applicable statutory and regulatory requirements, and other requirements essential for design and development.
   ISO 13485:2003: 7.2.1, 7.3.2
   21 CFR 820.30(c)

6. Review device specifications to confirm that design and development outputs meet design input requirements. Have the design outputs that are essential for the proper functioning of the device been identified?
   ISO 13485:2003: 7.3.3
   21 CFR 820.30(f), 820.30(d)

7. Confirm that risk analysis and risk control steps are completed and that the design and development outputs are compatible with the risk management data.
   ISO 13485:2003: 7.1, 7.3.5

21 CFR 820.30(g)

8. Determine that the intended use(s) have been identified. Confirm that design validation data show that the approved design meets the requirements for the specified application or intended use(s).
   ISO 13485:2003: 7.3.6
   21 CFR 820.30(g)

9. Confirm that clinical evaluations and/or evaluation of the medical device performance were performed if required by national or regional regulations.
   ISO 13485:2003: 7.3.6

   Note: FDA reviews and monitors clinical studies during special inspections specifically for this purpose, not during regulatory audits of quality systems.

10. If the device includes software, confirm that the software was part of the validation.
    ISO 13485:2003: 7.3.1, 7.3.6
    21 CFR 820.30(g)

11. Confirm that design changes were controlled and verified or where appropriate validated and that design changes have been addressed by the appropriate risk management steps.
    ISO 13485:2003: 7.1, 7.3.5, 7.3.7
    21 CFR 820.30(i), 820.70(b), 820.30(g)

12. Confirm that design reviews were conducted.
    ISO 13485:2003: 7.3.1, 7.3.4
    21 CFR 820.30(e)

13. Confirm that design changes ha ve been reviewed for the effect on components and product previously made and delivered, and that records of review results are maintained.
    ISO 13485:2003: 7.3.7
    21 CFR 820.30(i), 820.70(b)

14. Determine if the design was correctly transferred to production
    ISO 13485:2003: 7.3.1
    21 CFR 820.30(h)

Evaluate the „Design and Development“ subsystem for adequacy based on findings.

6.3 Technical Files*

GOAL: The purpose of auditing the technical files is to confirm that the manufacturer ensures that products will be safe and effective.

Major Steps: The following major steps serve as a guide in the audit of the ”Technical Files“ subsystem:

1. Verify if there are documents needed by the organization to ensure planning, operation and control of its processes.
   ISO 13485:2003: 4.2.1d
   21 CFR 820.180, 820.181, 820.184, 820.186

2. Select documents/documentation for product(s)
   Criteria for selection:

   - single product focus
   - risk based
   - based on complaints or known problems
   - most recent project
   - cover product range

3. For the product(s) selected verify that documentation includes:

   - a general description of the product including intended use(s) and any variants, accessories, or other devices used in combination with the selected product(s)
   - design specifications, including the standards applied, results of risk analysis
   - fulfilment of the principal requirements
   - techniques used to verify the design and to validate the product(s)
   - clinical data
   - description of sterilization method and validation – if applicable
   - instruction manual(s)
   - labelling
   - major subcontractors

   ISO 13485:2003: 7.1, 7.2, 7.3.3
   21 CFR 820.30(d), 820.30(g), 820.30(f), 820.181, 820.50, 820.75

Evaluate the„Technical Files“ subsystem for adequacy based on findings.

6.4 Production Processes *

GOAL: The purpose of auditing the production process (including testing , infrastructure, facilities and equipment) is to confirm that manufactured products meet specifications.

Major Steps: The following major steps serve as a guide in the audit of the “Production Process“ subsystem:

1. Verify that the product realization processes are planned – including the controlled conditions.
   ISO 13485:2003: 7.1
   21 CFR 820.70, 820.70(c)

2. Verify that the planning of product realization is consistent with the requirements of the other processes of the quality management system.
   ISO 13485:2003: 7.1
   21 CFR 820.30, 820.50, 820.80, 820.181

3. Select one or more processes for review
   Criteria for selection:
   - CAPA indicators of process problems
   - risk based: use of the process for manufacturing higher risk products
   - degree of risk of the process to cause product failure
   - most recent project: the manufacturer's lack of familiarity and experience with the process
   - use of the process in manufacturing multiple products
   - processes not covered during previous audits

   Note: For auditing a sterilization process see **Appendix 3**

4. Verify that the processes are controlled and monitored and operating within specified limits.
   ISO 13485:2003: 7.5
   21 CFR 820.50, 820.70(a), 820.70(c), 802.70(e), 820.70(f), 820.70(g), 820.70(h), 820.72, 820.75(b), 820.80

5. Verify that the equipment used has been adjusted, calibrated and maintained.
   ISO 13485:2003: 7.5
   21 CFR 820.70(g)(3), 820.72(a), 820.70(g)(1)

6. Verify that the processes have been validated if the result of the process cannot be verified.
   ISO 13485:2003: 7.5.2
   21 CFR 820.75

7. Determine the linkages to other processes
   ISO 13485:2003: 4.1, 4.2
   21 CFR 820.20, 820.25, 820.30, 820.40, 820.72, 820.90, 820.100, 820.180

8. Verify that personnel are appropriately qualified and trained to implement/maintain the processes
   ISO 13485:2003: 6.2.2
   21 CFR 820.20 (b)(2), 820.25, 820.70, 820.70(d), 820.75(b)(1)

9. Verify that the infrastructure and the work environment are adequate
   ISO 13485:2003: 6.3, 6.4
   21 CFR820.70(c), 820.70(g), 820.70(f)

10. Determine that the verification of purchased products is adequate
    ISO 13485:2003: 7.4.3
    21 CFR 820.50(a)(2), 820.80(b)

11. If the process is software controlled verify that the software is validated
    ISO 13485:2003: 7.5.2.1
    21 CFR 820.70(i)

12. Verify that the control of the monitoring and measuring devices is adequate.
    ISO 13485:2003: 7.6
    21 CFR 820.72,

13. Verify that the system for monitoring and measuring of products is adequate and that the monitoring and measuring devices used are adequately controlled
    ISO 13485:2003: 7.6, 8.2.4
    21 CFR 820.72, 820.80(c), 820.80(d)

14. Verify that the arrangement for control of non-conforming products is adequate
    ISO 13485:2003: 8.3
    21 CFR 820.90

Evaluate the "Production Processes" subsystem for adequacy based on findings.

6.5 Corrective and Preventive Actions – CAPA*

GOAL: The purpose of auditing the CAPA subsystem (including reporting / tracking) is to confirm that information is collected and analyzed to identify product and quality problems that these are investigated, and appropriate and effective corrective and preventive actions are taken.

Major Steps: The following major steps serve as a guide in the audit of the „Corrective and Preventive Actions - CAPA" subsystem:

1. Verify that CAPA system procedure(s) which address the requirements of the quality system have been established and documented.
   ISO 13485:2003: 4.1, 4.2, 8.5
   21 CFR 820.100(a)

2. Verify that the data received by the CAPA subsystem are complete, accurate and recorded in a timely fashion.
   ISO 13485:2003: 8.4, 8.5
   21 CFR 820.100(a)(1)

3. Determine if appropriate sources of product and quality problems have been identified, including sources which may show unfavourable trends. Confirm that data from these sources are analyzed, using valid statistical methods where appropriate, to identify existing product and quality problems that may require corrective action.
   ISO 13485:2003: 8.1, 8.2.3, 8.4
   21 CFR 820.100(a), 820.100(a)(1) 820.250

4. Determine if failure investigations are conducted to identify the causes of non-conformities, where possible.
   ISO 13485:2003: 8.5.2
   21 CFR 820.100(a)(2)

5. Verify that controls are in place to prevent distribution of non-conforming products.
   ISO 13485:2003: 8.3
   21 CFR 820.90(b)

6. Confirm that corrective and preventive actions were implemented, effective, documented and did not adversely affect finished devices.
   ISO 13485:2003: 8.2.3 8.5.2, 8.5.3
   21 CFR 820.100(a)(3), 820.100(a)(5), 820.100(a)(4), 820.100(b)

7. Determine if information regarding nonconforming product and quality problem and corrective and preventive actions has been supplied to management for management review.
   ISO 13485:2003: 5.6.3
   21 CFR 820.100(a)(7)

8. Verify that medical device reporting is done according to the applicable regulatory requirements.
   ISO 13485:2003: 8.5.1
   21 CFR 803.

9. Confirm that the manufacturer has made effective arrangements for handling complaints and investigation of advisory notices/recalls with provision for feed back into the corrective and preventive action subsystem.
   ISO 13485:2003: 7.2.3, 8.2.1
   21 CFR 820.100**;** 820.198**,**

Evaluate the ”Corrective and Preventive Actions“ subsystem for adequacy based on findings.

6.6 Purchasing Control

For virtual manufacturers *
* = This subsystem is a main subsystem for virtual manufacturers

GOAL: The purpose of auditing the purchasing control activities is to ensure that products, components, materials and services supplied by the subcontractor are in conformity. This is particularly important when finished products and/or sterilization services are purchased.

Major Steps: The following major steps serve as a guide in the audit of the Purchasing Control Subsystem:

1. Verify that procedures for conducting supplier evaluations have been established and are being implemented.
   ISO 13485:2003: 7.4.1
   21 CFR 820.50

2. Confirm that the manufacturer evaluates suppliers for their ability to meet specified requirements.
   ISO 13485:2003: 7.4.1
   21 CFR 820.50(a)(1)

3. Confirm that the manufacturer assures the adequacy of specifications for products and services that suppliers are to provide.
   ISO 13485:2003: 7.4.2
   21 CFR 820.50(b)

4. Confirm that records of supplier evaluations are maintained.
   ISO 13485:2003: 7.4.1
   21 CFR 820.50(a)(3)

5. Determine that the verification of purchased products is adequate
   ISO 13485:2003: 7.4.3
   21 CFR 820.50(a)(2), 820.80(a), 820:80(b)

Evaluate the ”Purchasing Controls“ subsystem for adequacy based on findings.

6.7 Documentation and Records

GOAL: The purpose of auditing the records and documentation is to ensure that the relevant documents are controlled within the manufacturer and that the relevant records are available to the regulatory body.

Major Steps: The following major steps serve as a guide in the audit of the Documentation and Records Subsystem:

1. Verify that procedures have been established for the identification, storage, protection, retrieval, retention time and disposition of documents and records.
   ISO 13485:2003: 4.2.3, 4.2.4
   21 CFR 820.180, 820.180(b)

2. Confirm that documents and changes are approved prior to use.
   ISO 13485:2003: 4.2.3
   21 CFR 820.40(a), 820.40(b)

3. Confirm that current documents are available where they are used and that obsolete documents are no longer in use.
   ISO 13485:2003: 4.2.3
   21 CFR 820.40(a)

4. Verify that required documents and records are being retained for the required length of time.
   ISO 13485:2003: 4.2.1, 4.2.4
   21 CFR 820.100(b), 820.180(b), 820.181, 820.184, 820.186, 820.198(a), 820.200(d)

Evaluate the ”Documentation and Records“ subsystem for adequacy based on findings.

6.8 Customer Requirements

GOAL: The purpose of auditing customer requirements is to ensure that customer requirements including regulatory requirements are met.

Major Steps: The following major steps serve as a guide in the audit of the Customer Requirements subsystem.

1. Review product requirements to verify that they address the intended use as well as customer and regulatory requirements.
   ISO 13485:2003: 7.2.2
   21 CFR 820.30(c), 820.30(d), 820.30(f), 820.30(g)

2. Confirm that incoming contracts and orders are reviewed to assure that any conflicting information is resolved and the manufacturer can fulfil the customer’s requirements.
   ISO 13485:2003: 7.2.2

3. Confirm that the manufacturer has made effective arrangements for handling communications with customers including documenting customer feedback to identify quality problems and provide input into the corrective and preventive action subsystem.
   ISO 13485:2003: 7.2.3, 8.2.1
   21 CFR 820.198, 820.100(a)(1)

Evaluate the ”Customer Requirements“ subsystem for adequacy based on findings.

Appendices

Appendix 1: Binomial Staged Sampling Plans
(taken from the Quality System Inspection Technique, QSIT (1999)

Table 1: Confidence Limit 95%
Table 2: Confidence Limit 99%

Table 1
Binomial Staged Sampling Plans
Binomial Confidence Levels

Confidence Limit .95≤		0 out of:	1 out of:	2 out of:
A	.30 ucl*	11	17	22
B	.25 ucl	13	20	27
C	.20 ucl	17	26	34
D	.15 ucl	23	35	46
E	.10 ucl	35	52	72
F	.05 ucl	72	115	157

Table 2
Binomial Staged Sampling Plans
Binomial Confidence Levels

Confidence Limit .99≤		0 out of:	1 out of:	2 out of:
A	.30 ucl*	15	22	27
B	.25 ucl	19	27	34
C	.20 ucl	24	34	43
D	.15 ucl	35	47	59
E	.10 ucl	51	73	90
F	.05 ucl	107	161	190

*ucl = Upper Confidence Level

CRC Handbook of Probability and Statistics: Second Edition

Binomial Sampling may be used when trying to make a decision about an endpoint that only has two potential outcomes (e.g., the record is compliant or the record is noncompliant).

Factors to consider when selecting a sampling table and sampling size may include the risk of the device or the records being sampled and the time the auditor has allocated to this part of the audit.

For the review of records regarding a low risk medical device, **Table 1** is recommended (95% Confidence), for the review of records regarding a high risk medical device **Table 2** is recommended (99% Confidence). Two examples are given:

Example 1:
The auditor plans to determine whether the sterilization process is monitored and controlled by reviewing sterilization records. The sterilization process is a high risk process, so the auditor uses sampling **Table 2** in **Appendix 1**. The auditor selects a sample of 24 sterilization batch records to review. All 24 records show that sterilization process was monitored and controlled and conducted at validated operating parameters. Based on **Table 2**, the auditor can be 99% confident that no more than 20% of the total population of sterilization records will show that the sterilization process was not conducted at the validated operating parameters.

Example 2:
The auditor is reviewing training records to determine whether employees have received training on recent revisions of the complaint handling procedures. The manufacturer makes computed tomography. Using **Table 1**, the auditor selects a sample consisting of training records for 17 employees. The auditor finds that one employee has not received training in the revised procedure. Using **Table 1**, the auditor can be 95% certain that not more than 30% of the employees have not received training in the newly revised procedure.

Appendix 2: Factors used to determine the audit duration

a) Factors which may increase the audit duration

i) Manufacturers using subcontractors to supply processes or parts that are critical to the function of the device and/or the safety of the user or finished products, including own label products. When the manufacturer cannot provide this evidence, then additional time should be allowed for each subcontractor to be audited.

ii) Manufacturers who install product on customer's premises.
Note: At least one customer site should be visited to audit the installation process or review a sample of the installation completion records.

iii) Audits conducted in a foreign language (see GHTF Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – General Requirements, Part 1, Supplement 1: Audit Language Requirements).

iv) Multipurpose audits required by the manufacturer.

b) Factors that may reduce the audit duration

i) Low and medium risk medical devices

ii) Any evidence of satisfactory audits from other third party or regulatory auditing organizations of subcontractors.

iii) The result of previous audits conducted by the auditing organisation show compliance with regulatory requirements.

iv) Reduction of the manufacturer product range since last audit.

v) Reduction of the design/or production process since last audit.

c) Multisite manufacturers

When multiple sites are involved, the manufacturer should define the activities that take place on each site.

When the sites operate different quality systems, for the purposes of estimating the audit duration each site should be regarded as a separate entity.

For manufacturers who have two or more manufacturing sites providing similar products or services in different locations, which are covered by a single quality system, the audit duration may be estimated in three steps:

a) Estimate the audit duration for each site separately, then total the auditor-days;

b) Add together the total number of staff for all sites, and then apply the IAF Guidelines;

c) Average these two results.

d) Other types of audits

There are a number of types of audits where the duration is less than that required for a full initial audit.
(See GHTF Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers Part 1- general requirements, SG4/N28R2 section 8).

The factors listed in this appendix should be considered when estimating audit duration for those other types of audits.

For partial audits, the duration should be calculated according to the number of quality subsystems that are to be examined. This could apply, for example, to re-audits conducted to verify corrective actions taken as a result of the initial audit, or to situations where the regulations only require a partial audit, e.g. Class 1 measuring devices in the EU.

In cases where significant changes have occurred to a manufacturer (see GHTF Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers Part 1- general requirements, section 8.3) additional time may be required.

Appendix 3: Sterilization Process

GOAL: The purpose of auditing the sterilization process (including testing, infrastructure, facilities and equipment) is to confirm that products subjected to the sterilization process are sterile.
ISO: 7.5.1.3
21 CFR 820

Major Steps: The following major steps serve as a guide in the audit of sterilization processes under the Production Process subsystem:

1. Determine that the sterilization processes are planned – including the controlled conditions.
   ISO 13485:2003: 7.1, 7.5.1.3
   21 CFR 820.70(a), 820.70(c), 820.70(d), 820.70(f)

2. Determine that the planning of product sterilization is consistent with the requirements of the other processes of the quality management system.
   ISO 13485:2003: 7.1. 7.5.1.3
   21 CFR 820.181, 820.50

3. Determine that records of process parameters for the sterilization process for each sterilization batch are maintained and are traceable to each production batch.
   ISO 13485:2003: 7.5.1.3
   21 CFR 820.184

4. Select a sterilization process(es) for review. If there is more than one sterilization process use the following criteria
   - Process used for highest risk device
   - Process used for the largest number of devices
   - Process that is most difficult to control

5. Determine that the sterilization process has been validated and review the validation for adequacy. Validation includes qualification of the sterilizer. Check that validation is up-to-date.
   ISO 13485:2003: 7.5.2.1
   21 CFR 820.70(g), 820.75(a),

6. Determine that biological indicators are handled appropriately and validated.
   ISO 13485:2003: 8.2.3
   21 CFR 820.70(a), 820.80, 820.140, 820.150

7. Determine that the process is controlled and monitored including product bioburden. Verify that configuration of loads comply with validated configurations.
   ISO 13485:2003: 7.5.1.3
   21 CFR 820.50, 820.70(a), 820.70(c), 820.70(e), 820.70(f), 820.70(g), 820.70(h), 820.72, 820.75(b), 820.80

8. Determine that the process is operating within specified limits.
   ISO 13485:2003: 7.5.1.3
   21 CFR 820.70(a), 820.70(c), 820.70(e), 820.70(h), 820.75(b)

9. If data indicates that the process does not always meet process parameters, determine that nonconformances are handled appropriately and investigated and appropriate corrections and corrective actions are taken to address nonconformances.
   ISO 13485:2003: 8.1, 8.2.3, 8.3, 8.4, 8.5.2
   21 CFR 820.100(a)(2), 820.90, 820.100(a)(4), 820.100(a)(5)

10. If the sterilization process is software controlled, determine that the software is validated.
    ISO 13485:2003: 7.5.2.1
    21 CFR 820.70(i)

11. Determine that the equipment used has been adjusted, calibrated and maintained. ISO
    ISO 13485:2003: 7.5, 7.6
    21 CFR 820.72, 820.70(g)

12. Determine that personnel are appropriately qualified and trained to validate, implement and maintain the process.
    ISO 13485:2003: 6.2
    21 CFR 820.75(b)(1)

Evaluate the sterilization process for adequacy as part of the evaluation of the Production Processes subsystem.